Remarks

Claims 1-16 were pending in the subject application. By this Amendment, claims 1, 2, 4, 7, 9, 13, and 14 have been amended, claims 5, 6, 8, 10-12, 15, and 16 have been cancelled, and new claims 17-22 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-4, 7, 9, 13, 14, and 17-22 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

The applicant and the applicant's representative wish to thank Examiner Marvich for the courtesy of the telephonic interviews conducted with the undersigned on August 23, 2005, regarding the priority of claims 2-4, 13, and 14, and on October 12, 2005, regarding the rejections under 35 U.S.C. §102 and §112, first paragraph, as set forth in the subject application and the parent application, U.S. Serial No. 10/049,502. The remarks and amendments set forth herein are consistent with the substance of the interview and are believed to address the outstanding issues as discussed during the interview.

Submitted herewith is a supplemental Information Disclosure Statement (IDS), accompanied by the form PTO/SB/08 and copies of the references listed therein. The applicant respectfully requests that the references listed on the form PTO/SB/08 be considered and made of record in the subject application.

By this Amendment, the applicant has amended claims 1, 2, 4, 7, 9, 13, and 14 and added claims 18-22. Support for the amendment to claim 1 can be found, for example, at page 9, lines 25-31; page 10, lines 1-17; page 14, lines 10-26; page 15, lines 29-31; page 16; and page 17, lines 1-6, of the subject specification. Support for the amendments to claims 2, 4, 13, and 14, can be found at page 15, lines 29-31; page 16, lines 1-9; and page 17, lines 7-8, of the subject specification. Support for claim 7 can be found, for example, at page 9, lines 25-31, of the specification, and claim 5 as originally filed. Support for claim 9 can be found, for example, at page 15, lines 29-31, and page 16, lines 1-5, of the subject specification. Support for claims 17 and 18 can be found, for example, at page 15, lines 1-14; page 8, lines 25-31; and page 9, lines 1-5, of the subject specification. Support for claim 19 can be found, for example, at page 14, lines 16-26, of the subject specification. Support

for claims 20-21 can be found, for example, at page 10, lines 10-12, of the subject specification. Support for claim 22 can be found, for example, at page 8, lines 25-31; page 9, lines 1-5, page 10, lines 10-12; page 15, lines 1-14; and page 34, lines 13-24 (Example 19), of the subject specification.

The Examiner has objected to Figure 7B as failing to show any details as described in the specification. The applicant notes that the photographs that are in the Image File Wrapper on PAIR, are much less clear than the photographs that the applicant provided when the application was filed. The photographs that the applicant provided appear to have been scanned into the Image File Wrapper using a poor resolution setting. Submitted herewith are true and exact copies of Figures 7A-7C on high-quality photo paper.

Claims 1, 2, 5, 7, and 9 have been provisionally rejected under the judicially created doctrine of "obviousness-type" double patenting as being unpatentable over claim 8 of co-pending Application No. 10/049,502 (USF-T144X; your ref. 00A019PRCWOUS). The applicant respectfully asserts that the claims are not obvious over the cited patent application. However, in order to expedite prosecution of the subject application, the applicant has submitted a Terminal Disclaimer with this Amendment, which obviates this rejection. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1-5, 7-10, and 12-14 have been rejected under 35 U.S.C. §112, first paragraph, as lacking sufficient written description. The Office Action indicates that the subject specification does not provide a sufficient written description of the recited genus of RhoB variant proteins. The applicant respectfully submits that the subject specification provides a sufficient written description of the claimed subject matter. However, in order to expedite prosecution of the subject application, the applicant has amended claims 1, 4, and 7 to remove reference to variants. Furthermore, the applicant has amended claim 1 to recite that a nucleic acid sequence encoding wild-type (WT) RhoB protein is administered. Support for this amendment can be found, for example, at page 8, lines 20-23, of the subject specification. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 1-5, 7-10, 13, and 14 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The applicant respectfully submits that the subject specification enables the method of the subject invention. However, as discussed during the

telephonic Examiner interview, the applicant has amended claim 1 to recite a method for inhibiting the growth of a tumor in a mammal, comprising administering an effective amount of a nucleic acid sequence encoding wild-type RhoB protein to cells associated with the tumor, wherein the nucleic acid sequence is expressed in the cells and the RhoB protein inhibits at least one activity of the cells selected from the group consisting of migration, invasion, and metastasis.

The Office Action indicates that the subject specification does not provide sufficient guidance resolving issues associated with *in vivo* delivery of nucleic acids encoding RhoB, particularly for human application. Submitted herewith for the Examiner's consideration is Exhibit A, which provides further evidence for the potent tumor suppressive activity of RhoB and confirms the ability to deliver nucleic acids encoding RhoB *in vivo*. The experimental data presented in Exhibit A demonstrates that nucleic acids encoding wild-type RhoB can be delivered within a human lung tumor growing in a mouse model, resulting in inhibited tumor growth. Previously, Dr. Sebti's laboratory showed that forced expression of RhoB in human cancer cells suppresses tumor growth *ex vivo*. As described at pages 16 and 17 of the parent application, U.S. Serial No. 10/049,502, (pages 5-7 of U.S. Publication No. 20030018003, which is submitted with the attached IDS), this was done by stably expressing RhoB in human pancreatic cancer cells (Panc-1 cells), subcutaneously injecting these cells into mice, and showing that the RhoB-expressing human cancer cells did not grow. This previous experiment provided evidence for the potent tumor suppressive activity of RhoB. An experiment was then designed to demonstrate that tumor suppression can be achieved by delivering RhoB *in vivo* directly into growing tumors. Under the direction of Dr. Sebti, a nucleic acid sequence encoding wild-type RhoB was cloned into an adeno-viral vector, as taught at page 10 of the subject application and page 3 (paragraphs 0019-0020) of U.S. Publication No. 20030018003. Human lung cancer A-549 cells were injected subcutaneously into the flanks of female athymic nude mice, using the mice as a human tumor xenograft model. When tumors reached an average volume of 150-200 mm^3, approximately $5x10^{10}$ adenoviral particles expressing adenoviral-RhoB, adeno-RhoA, or adenovector (vector alone), were injected everyday intra-tumorally for 12 days (150 µl per injection). As is evident from the graph (Exhibit A), A-549 tumors injected intra-tumorally with vector alone grew from 200 mm^3 to 800 mm^3 over a period of 17 days. In contrast, A-549 tumors injected with adeno-RhoB grew to only 400 mm^3. Tumors injected with adeno-RhoA grew to 900 mm^3. Thus, in

this experiment, it was confirmed that injection of human tumors in nude mice *in vivo* with adeno-RhoB results in reduced tumor growth. Furthermore, based on the *in vitro* and *in vivo* experimental data provided at pages 21-34 (Examples 1-19) of the subject application, and pages 5-7 of U.S. Publication No. 20030018003, which characterize the mechanism of RhoB's potent tumor suppressor function, it is reasonable to expect that the described underlying physiological effects occur *in vivo*, and correlate with suppressed or inhibited tumor growth in mammals. The applicant respectfully submits that one of ordinary skill in the art would accept the *in vitro* and *in vivo* data presented in the subject application and Exhibit A as reasonably predictive of RhoB's therapeutic benefit (*e.g.*, suppression of tumor cell growth) in mammals, including humans.

In regard to animal models, the applicant submits that all that is required by the patent laws is that a "reasonable correlation" exist between the scope of the claims and the scope of enablement. *In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) and MPEP 2164.02. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 224 USPQ 739, 747 (Fed. Cir. 1985):

> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

If a particular model is recognized as correlating to a specific condition, then it should be accepted as such unless there is evidence that the model does not correlate. Since the initial burden is on the Examiner to give reasons for lack of enablement, reasons must also be given for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example.

The nude mouse tumor xenograft model is an art-recognized animal model of cancer. The human tumor xenograft model utilized in the above-described experiment represents a stringent model for assessment of the therapeutic potential of RhoB. While it is true that there is a continued need to refine and improve pre-clinical cancer models to recapitulate the clinical situation in humans to the extent possible, at the time the subject application was filed, human tumor xenograft models were recognized by those in the field as one of the best tools for conducting pre-clinical *in vivo* analyses of intact human tissue. Submitted with the attached IDS are Kerbel, R.S., *Cancer Biology & Therapy*, July/August 2003, 2:4:Suppl. 1:S134-139; Caponigro, F., *Anti-Cancer Drugs*, 2002,

13:891-897; End, D.W. *et al.*, *Cancer Research*, 2001, 61:131-137; and Shi, B. *et al.*, *Cancer Chemother. Pharmacol.*, 2000, 46:387-393. As stated in the Kerbel publication,

> Close inspection of retrospective and prospective studies in the literature, however, reveals that human tumor xenografts—even non metastatic ectopic/subcutaneous 'primary' tumor transplants—can be remarkably predictive of cytotoxic chemotherapeutic drugs that have activity in humans, when the drugs are tested in mice using pharmacokinetically clinically equivalent or 'rational' drug doses. (Kerbel, abstract; emphasis added)

Disparities between responses observed during pre-clinical studies in the human tumor xenograft model and studies in human cancer patients often attract considerable attention and garner some skepticism. However, when the advanced condition of those patients enrolled in clinical trials is considered in proper context, the clinical predictive value of the pre-clinical human tumor xenograft model must be acknowledged. As stated by the Kerbel publication,

> ...this skepticism may not always be justified when one takes into account, in retrospect, a crucial and fundamental difference between virtually all published experimental mouse therapy studies and corresponding clinical trials, and it is this: in most phase I, II and III clinical trials the patients being treated have advanced, high-volume metastatic disease whereas most mouse studies do not test the effects of therapy on advanced metastatic disease, but rather on a primary tumor transplant or spontaneously arising primary tumor, or microscopic, low-volume metastatic disease (Lee Ellis, personal communication). (Kerbel, page S137, emphasis added)
> ... It is also time to reexamine some of the current dogmas regarding mouse models of cancer. First, human tumor xenografts can be surprisingly predictive of clinical activity, and in some cases this includes subcutaneous/ectopic transplants. The wisdom of the rush towards exclusive use of much more expensive transgenic oncomouse models for drug therapy testing can be questioned, especially when such tumors fail to express the most critical element of malignant disease—ability to metastasize, and the fact that less expensive transplantable tumor models are available which work—if used appropriately. (Kerbel, page S139, emphasis added)

The Caponigro F., End D.W. *et al.*, and Shi B. *et al.* publications demonstrate a correlation between results from pre-clinical human tumor xenograft studies and results from human clinical trials for two different compounds, R115777 and SCH-66336, known as farnesyl transferase inhibitors (FTI). FTI are currently believed to target RhoB (Prendergast and Rane, *Expert Opin. Investig. Drugs*, 2001, 10(12):2105-2116; cited in the Office Action). Advancement of a candidate drug from pre-

clinical testing in the laboratory to testing in Phase II clinical trials is based on the assumption that drug activity in cancer models translates into at least some efficacy in human patients, *i.e.*, that cancer pre-clinical laboratory models are clinically predictive. The human tumor xenograft model was art-recognized as an acceptable pre-clinical model for cancer at the time the application was filed, and remains in use today. One of ordinary skill in the art would expect that the experimental results obtained using this model would reasonably correlate with a therapeutic benefit in human patients. Thus, the applicant respectfully submits that the models within the specification and Exhibit A are sufficiently predictive of tumor growth in mammals. As such, the pending claims are commensurate in scope with the experimental findings of the instant disclosure and enabled thereby.

In addition to adenoviral-mediated gene delivery, other techniques for RhoB delivery may be employed, as taught in the subject application. For example, other viral and non-viral vectors may be used to deliver nucleic acid constructs encoding RhoB to tumor cells, resulting in RhoB expression. Furthermore, tissue-specific promoters may be used, or as taught at page 10, lines 10-15, of the subject specification, event-specific promoters may be utilized with nucleic acid constructs encoding RhoB to further optimize and localize expression within the diseased tissues. Submitted with the attached IDS is the Robson *et al.* publication, which reviews various methodologies and vectors available for delivering and expressing nucleic acids *in vivo* for the purpose of treating cancer (Robson, T. Hirst, D.G., *J. Biomed. and Biotechnol.*, 2003, 2003(2):110-137). Among the various targeting techniques available, transcriptional targeting using tissue-specific and event-specific transcriptional control elements is discussed. For example, Table 1 at page 112 of the Robson *et al.* publication lists several tissue-specific promoters useful in cancer therapy, many of which were available at the time the patent application was filed. Tables 2-4 of the Robson *et al.* publication list tumor-specific promoters, tumor environment-specific promoters, and exogenously controlled inducible promoters, many of which were available at the time the patent application was filed. The successful delivery and expression of the p53 tumor suppressor gene *in vivo* has been documented (Horowitz, J. *Curr. Opin. Mol. Ther.*, 1999, 1(4):500-509; Von Gruenigen, V.E. *et al. Int. J. Gynecol. Cancer*, 1999, 9(5):365-372; Fujiwara, T. *et al.*, *Mol. Urol.*, 2000, 4(2):51-54, respectively). As the Examiner is aware, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already

available to the public. *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 USPQ 481, 489 (Fed. Cir. 1984). In view of the means available for delivery and expression of nucleic acids to a human or non-human mammal *in vivo*, and the success demonstrated with these systems, one of ordinary skill in the art would expect that the obstacles to RhoB gene delivery set forth in the Office Action can be addressed by optimization, rather than undue experimentation.

At pages 8 and 9 of the Office Action, the Examiner raises several issues such as toxicity, route of delivery, potential cancer-inducing properties of retroviral vectors, *etc.* The applicant respectfully submits that an application for patent is not required to show that a claimed method of treatment of a disease condition results in a cure of that disease condition, or even that clinical efficacy is achieved. The Federal Circuit has made it clear that the showing for therapeutic utility that is sufficient to satisfy the patent laws is not to be confused or equated with the showing required by the Food & Drug Administration for drugs, medical devices, and procedures. *Scott v. Finney*, 32 USPQ2d 1115 (Fed. Cir. 1994) and Manual of Patent Examining Procedure 2164.05. Given the state of the art as demonstrated by the scientific publications submitted herewith, and the information provided in the subject specification and the experimental results obtained therewith, one of ordinary skill in the art can deliver nucleic acids encoding wild-type RhoB to tumor cells in a mammal without resort to undue experimentation. Thus, the applicant respectfully submits that the subject specification enables the methods as currently claimed.

The proper standard for compliance with the enablement requirement is not absolute predictability but objective enablement. Evidence provided by the applicant need not be conclusive but merely convincing to one of skill in the art (see MPEP 2164.05). In other words, a patent specification need not set forth clear and convincing evidence "proving" its conclusions. Rather, the applicant's statements and assertions are to be taken as true, and rejected only if the underlying facts are found to be untruthful or inaccurate, *i.e.*, only if the asserted claim is "incredible" or "impossible." *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971). The experimental evidence in the subject specification is sufficiently compelling and fully supports the assertion that delivery of nucleic acids encoding wild-type RhoB reduces tumor growth in mammals. The experimental data

provided in the subject application, U.S. Publication No. 20030018003, and Exhibit A show that nucleic acids encoding wild-type RhoB can be successfully delivered using methods for gene delivery taught in the subject application and/or known to those skilled in the art at the time the application was filed.

The applicant respectfully submits that, in view of the disclosure of the subject specification as originally filed, and in view of the experimental results developed using those techniques that are described in the specification and/or known to those of ordinary skill in the art, methods for delivering nucleic acids encoding wild-type RhoB to tumor cells *in vivo* are fully enabled.

Accordingly, the applicant respectfully submits that, given the teaching of the specification and the state of the art, one of ordinary skill in the art could carry out the claimed method without the need for undue experimentation. In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 1-5, 7-9, and 12-14 have been rejected under 35 U.S.C. §102(b) as being anticipated by Du *et al.* (*Mol. Cell. Biol.*, 1999, 19:1831-1840) as evidenced by Prendergast *et al.* (*Expert Opin. Investig. Drugs*, 2001, 10:2105-2116). The applicant respectfully submits that the Du *et al.* publication does not teach the method of the invention as currently claimed. As indicated above, the applicant has amended claim 1 to recite a method for inhibiting the growth of a tumor in a mammal, comprising administering an effective amount of a nucleic acid sequence encoding wild-type RhoB protein to cells associated with the tumor. The claims no longer refer to RhoB variants. In contrast, as discussed during the telephonic Examiner interview, the genetic construct used in the Du *et al.* publication was a chimera (plasmid zeoCMV-HA-RhoB-GG) composed of a portion of RhoB and a portion of RhoA. The composition of the construct is described at page 1832, column 1, first paragraph, of the Materials and Methods section, of the Du *et al.* publication. Furthermore, the applicant respectfully submits that the *in vitro* results reported in the cited reference using the described chimeric construct cannot be extrapolated to use of wild-type RhoB *in vivo* with any reasonable expectation of success.

As the Examiner is aware, to be anticipatory under 35 U.S.C. §102, a reference must disclose within the four corners of the document each and every element and limitation contained in the rejected claim. *Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ 2d 1001, 1010

(Fed. Cir. 1991). The applicant respectfully submits that the Du *et al.* publication does not teach or suggest every element of the applicant's claimed invention. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

Claims 1, 5, 7, 9, and 12 have been rejected under 35 U.S.C. §102(a) as being anticipated by Du and Prendergast (*Cancer Research*, 1999, 59:5942-5496). In addition, claims 13 and 14 are rejected under 35 U.S.C. §102(b) as being anticipated by Du and Prendergast. The applicant respectfully submits that the Du and Prendergast publication does not teach the method of the invention as currently claimed. As indicated above, the applicant has amended claim 1 to recite a method for inhibiting the growth of a tumor in a mammal, comprising administering an effective amount of a nucleic acid sequence encoding wild-type RhoB protein to cells associated with the tumor. The claims no longer refer to RhoB variants. In contrast, as discussed during the telephonic Examiner interview, the genetic construct used in the Du and Prendergast publication uses the HA-rhoB-GG insert from the construct described in Du *et al.* (*Mol. Cell. Biol.*, 1999, 19:1831-1840). The construct is described at page 5492, second column, first paragraph of the Materials and Methods section of the Du and Prendergast publication. Furthermore, the applicant respectfully submits that the *in vitro* results reported in the cited reference using the described chimeric construct cannot be extrapolated to use of wild-type RhoB *in vivo* with any reasonable expectation of success.

As indicated above, to be anticipatory under 35 U.S.C. §102, a reference must disclose within the four corners of the document each and every element and limitation contained in the rejected claim. The applicant respectfully submits that the Du and Prendergast publication does not teach or suggest every element of the applicant's claimed invention. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §102(a) and §102(b) is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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